

# PBPK Modeling of Ethylene Glycol and It's Metabolite, Glycolic Acid

Richard A. Corley, Ph.D.

Toxicology Forum

July 10-14, 2000

Aspen, CO

Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

screen 1

## Outline

---

- Driving forces for PBPK model development
- Metabolism and mode of action
- Model structure
- ADME parameter estimation
- Simulations of available *in vivo* data
- Ongoing research
- Conclusions to date

Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

screen 2

## Driving Forces for PBPK Model Development

- Metabolite (GA) is proximate developmental toxicant
  - non-linear metabolism
  - dose-rate/dose-route critical determinants
  - significant species differences
- Facilitate extrapolations
  - high-to-low dose
  - route-to-route
  - species-to-species
- Exposure assessment guidelines (e.g. RfC/RfD) encourage use of validated PBPK models

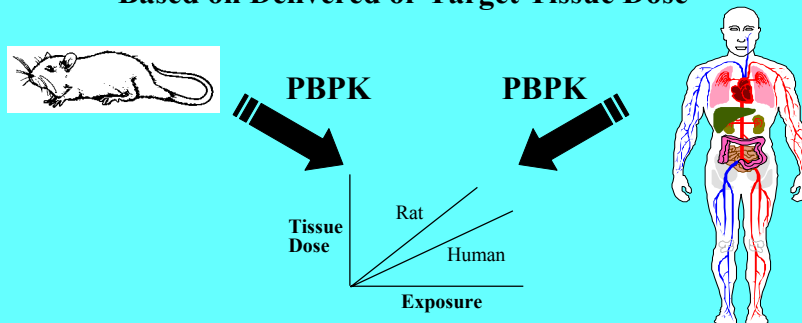
Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

version 3

## Animal-to-Human Extrapolation

Based on Delivered or Target Tissue Dose



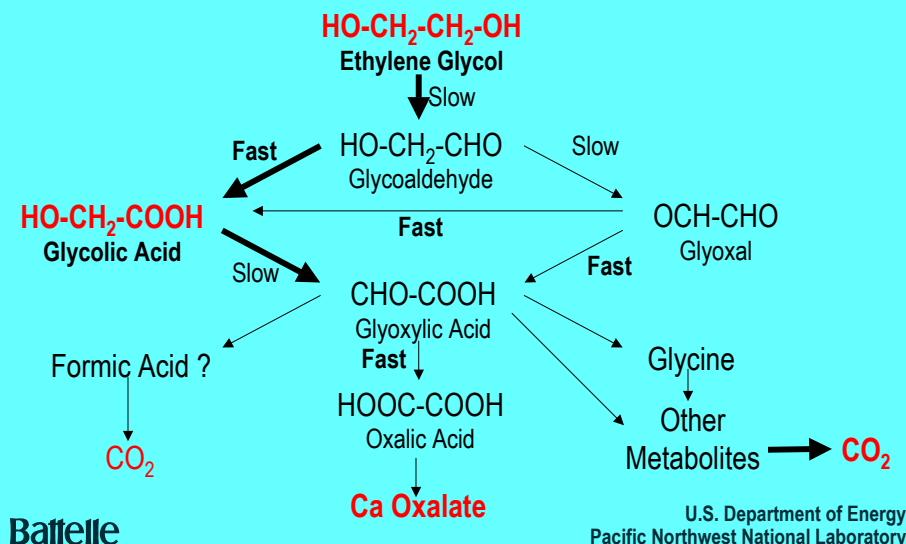
**Equivalent Tissue Dose = Equivalent Effect**

Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

version 6

## Metabolism of EG



## Metabolism and Kinetics Key for Toxicity

- Bioavailability
  - well-absorbed orally
  - poorly absorbed dermally
  - low vapor pressure limits vapor exposures
- Non-linear metabolism of glycolic acid
  - low doses (20-200 mg/kg)
    - GA minor (<5% of dose)
    - $\text{CO}_2$  major (30-40% of dose)
  - high doses (200 - 2000 mg/kg)
    - GA major (20-50% of dose)
    - $\text{CO}_2$  reduced (<25% of dose)

**Battelle**

U.S. Department of Energy  
Pacific Northwest National Laboratory

## Metabolism and Kinetics Key for Toxicity

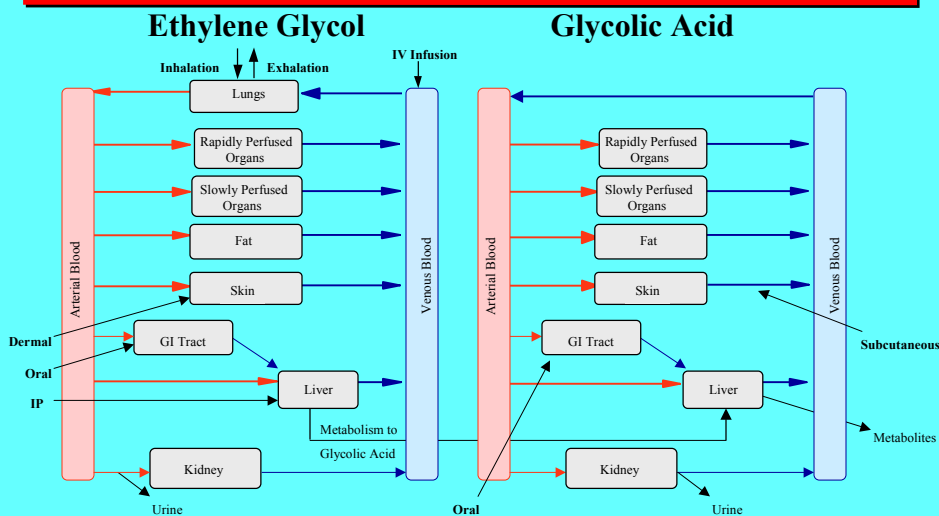
- Oxalic acid accounts for <2% of dose
- Other metabolites have very short  $t_{1/2}$ 's and are difficult to detect
- Several metabolites are also:
  - dietary constituents
  - water DBP's
  - products of endogenous biosynthesis

Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

version 7

## PBPK Model Structure



Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

version 8

## Parameter Estimation - ADME

---

- EG Blood:Air Partition coefficients
  - vial equilibration (rat & human  $\lambda \sim 17,500$ )
- First-order absorption for EG and GA
  - oral gavage, IP injection, SC injection
- IV injection direct input into venous blood
- Dermal absorption of EG (format of Jepson & McDougal, 1997)
- Inhalation of EG (format of Andersen et al., 1987)

Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

screen 9

## Parameter Estimation - ADME

---

- Partition coefficients
  - EG and GA tissue:saline by ultrafiltration ( $\lambda \sim \text{unity}$ )
  - GA in EEF & Embryos by ultrafiltration (in progress)
- Plasma protein binding
  - No evidence for GA protein binding in either rat or human plasma by ultrafiltration
  - Positive controls (phenol) consistent with published data

Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

screen 10

## Parameter Estimation - ADME

---

- EG metabolism
  - *In vitro* rat/rabbit/human liver slice studies for EG
    - rate constants resulted in underprediction of *in vivo* metabolism
  - First-order EG metabolism estimated from *in vivo*, female SD rat data (Pottenger et al., 1998)
  - Additional human/rat S9 comparisons (in progress)
- GA metabolism
  - *In vitro* rat/rabbit/human liver slice studies for GA
- Reduced metabolism of GA *in vivo* at >3 g/kg dose
  - Competitive inhibition of GA metabolism by EG incorporated

Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 11

## Parameter Estimation - ADME

---

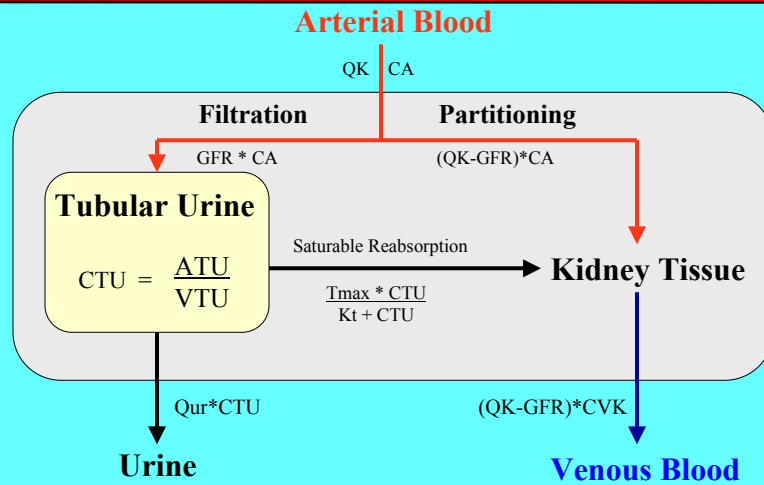
- Renal clearance estimated from *in vivo* studies
  - First-order clearance of EG from arterial blood
    - Female SD rats (Pottenger et al., 1998)
  - Higher clearance of GA in urine at doses >500 mg/kg
    - NOT associated with saturated protein binding
    - Non-linear clearance described by kidney model including
      - glomerular filtration
      - saturable reabsorption
        - Male Wistar rats (Richardson, 1973; Harris & Richardson, 1980)
        - Female SD rats (Pottenger et al., 1998)

Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 12

## GA Kidney Model



Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 13

## Simulations of Available Data

Battelle

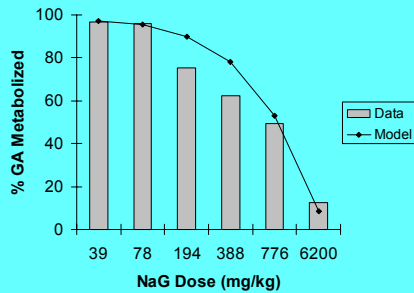
U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 14

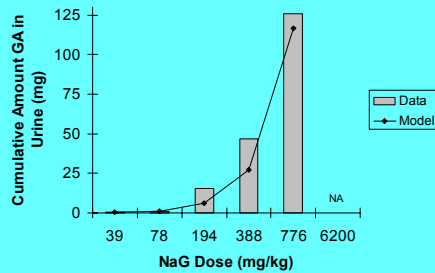
## Male Wistar Rat - Oral Gavage - NaG

(Richardson, 1973; Harris & Richardson, 1980)

### Metabolism of GA



### Urinary Clearance of GA



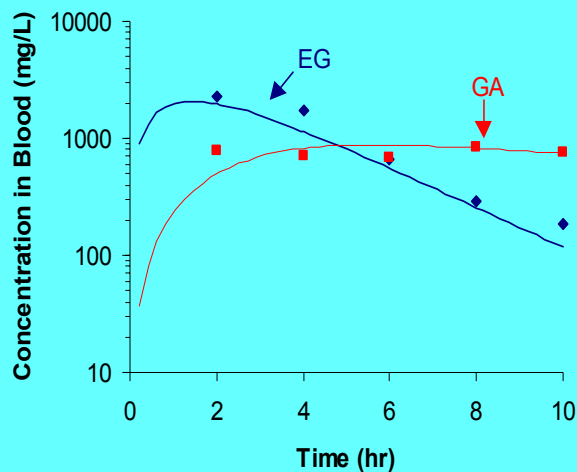
Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 15

## Male Wistar Rat - IP Injection - EG

2700 mg/kg (Chou & Richardson, 1978)



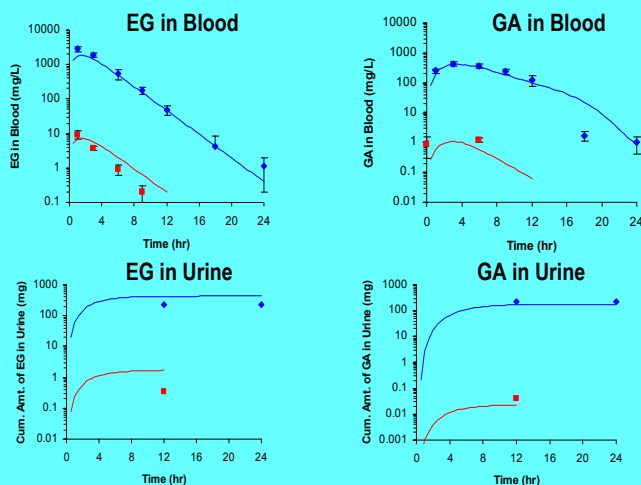
Battelle

Department of Energy  
Pacific Northwest National Laboratory

slide 16

## Female SD Rat - Oral Gavage - EG

10 and 2500 mg/kg (Pottenger et al., 1998)



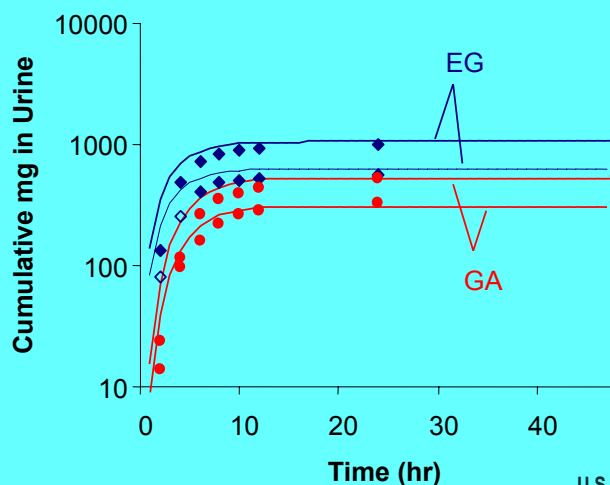
Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

10/08/17

## Male SD Rat - Oral Gavage - EG

3326 and 5544 mg/kg (Lenk et al., 1989)



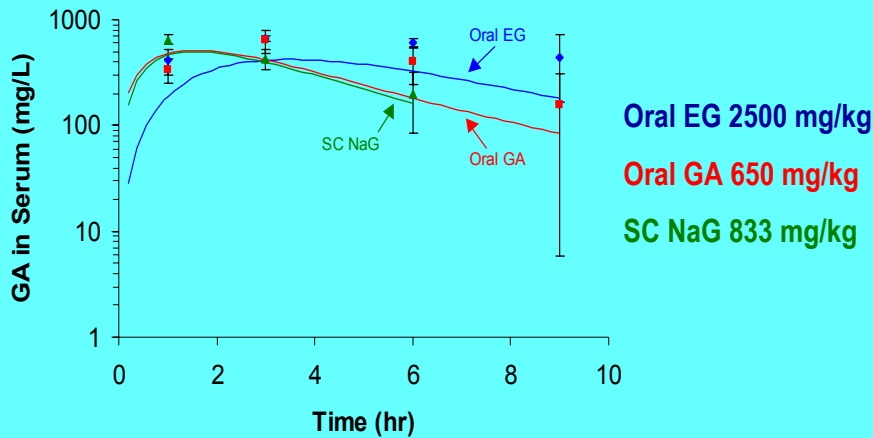
Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

10/08/15

## Pregnant SD Rat - Oral Gavage **EG**, **GA** - SC **NaG**

Carney et al., 1997



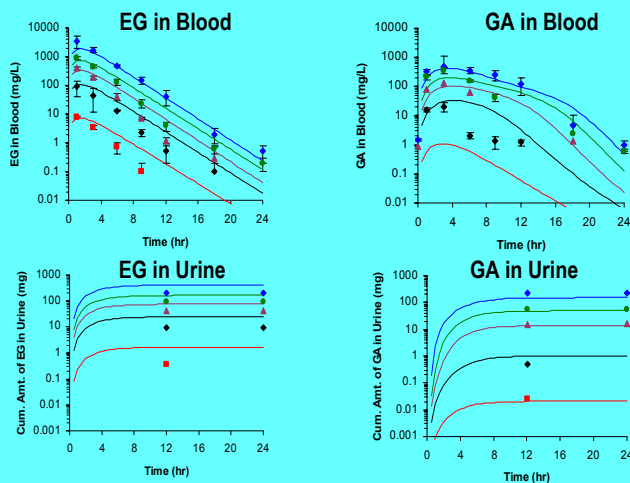
Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 19

## Pregnant SD Rat - Oral Gavage - **EG**

10, 150, 500, 1000 and 2500 mg/kg (Pottenger et al., 1998)



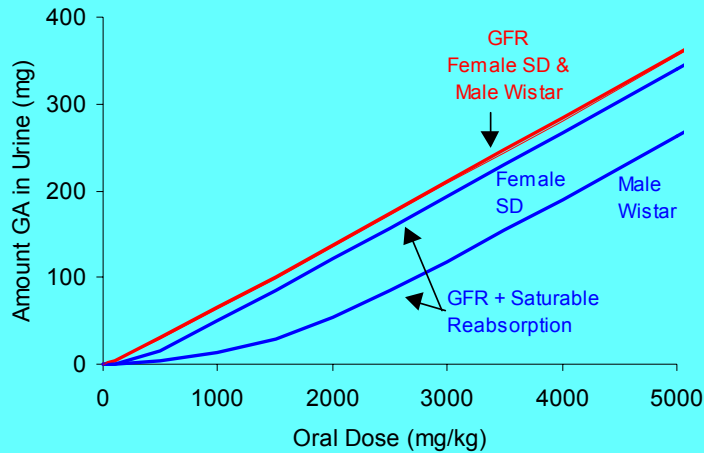
Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 20

## Strain Differences in Renal Clearance of GA

Female SD vs. Male Wistar Rats



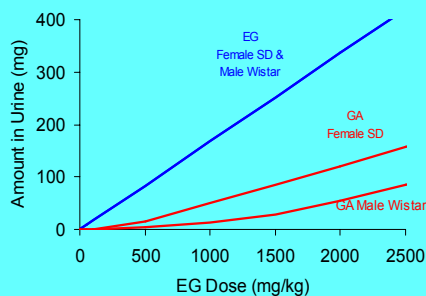
Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

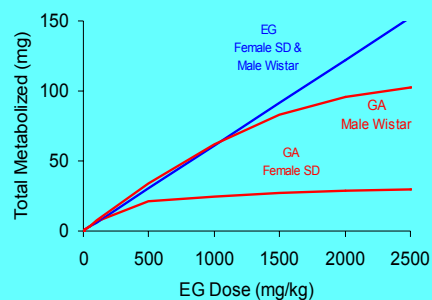
slide 21

## Dose-Response Oral Gavage Simulations Pregnant (gd10) SD vs. Male Wistar Rats

Urinary Clearance



Metabolism

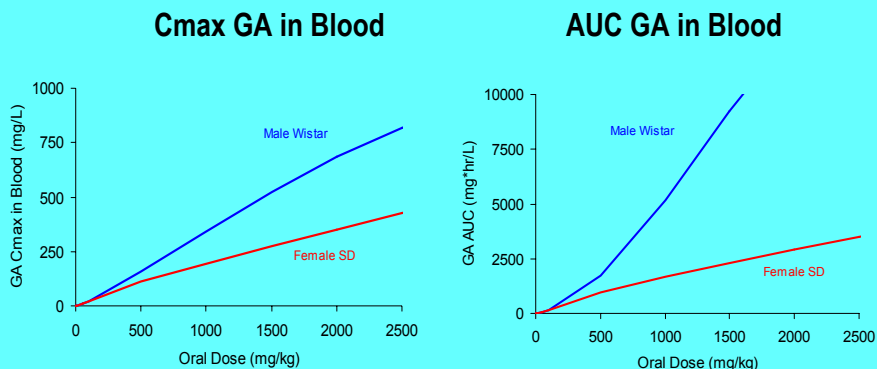


Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 22

## Dose-Response Oral Gavage Simulations Pregnant (gd10) SD vs. Male Wistar Rats



Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 23

## Ongoing Research

- Extend the model to the developing rat embryo
  - partition coefficients for GA in EEF and embryos
  - dose-rate kinetics of EG in pregnant SD rats (gd11)
    - constant infusion vs. oral gavage
- Extend the model to the human
  - additional rat/human S9 *in vitro* metabolism of EG
  - utilize existing human liver slice data with GA
  - human inhalation kinetic study (Filser)
  - maternal blood GA (Cmax, AUC) internal dose surrogate for developmental toxicity
  - human suicide kinetic data of limited use for validation

Battelle

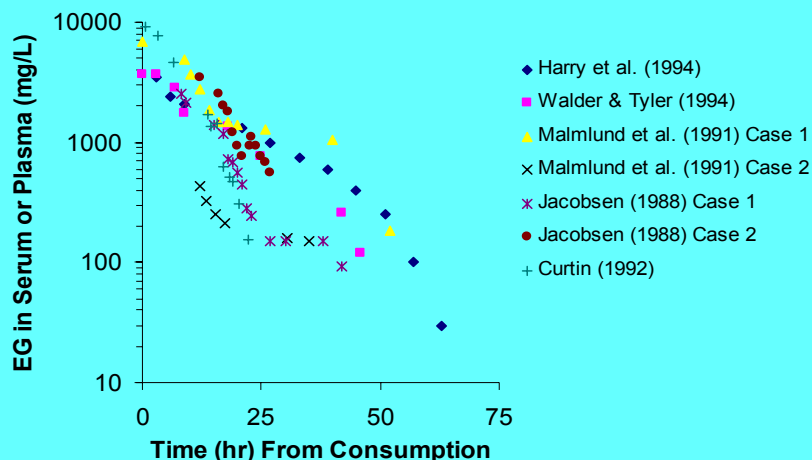
U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 24

## Human Attempted Suicide Case Reports

Doses Ranged From: ~1300 - 28,000 mg/kg

Treatments Ranged From: Gastric Lavage, Ethanol, Hemodialysis, 4-MP



Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

version 25

## Potential Impacts of PBPK and Mechanism Studies on Risk Assessment (e.g. RfC/RfD)

$$\text{RfC} = \frac{\text{HEC}}{\text{UF}_H \times \text{UF}_A \times \text{UF}_S \times \text{UF}_L \times \text{UF}_D \times \text{MF}}$$

$$\text{HEC} = \text{Animal NOAEL} \times \text{DAF}$$

### ■ Modify HEC

- Replace default dose-duration adjustment factor (DAF)
  - DAF not generally used in developmental toxicity
- calculate Human NOAEL based upon internal dose

### ■ Modify uncertainty factors

- e.g. animal to human ( $\text{UF}_A$ ), intra-human ( $\text{UF}_H$ )

Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

version 25

## Conclusions to Date

---

- Variety of rat kinetic data following several routes of administration and dose levels well-simulated
  - No impact of pregnancy on kinetics of EG and GA
  - Higher internal dose of GA in male Wistar rats than male and female SD or F344 rats
- Non-linear clearance of GA in urine
  - NOT plasma protein binding-dependent
  - described by saturable reabsorption in kidney tubules
- Non-linear maternal blood GA kinetics well-described
  - consistent with developmental toxicity

**Battelle**

U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 27

## Extra Slides

---

**Battelle**

U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 28

## Blood:Air Partition Coefficients

	<b>EG</b>	<b>EGME<sup>a</sup></b>	<b>EGBE<sup>a</sup></b>	<b>MeOH<sup>b</sup></b>	<b>EtOH<sup>c</sup></b>
Rat blood:air	<b>17,902</b>	---	---	1349	2,140
Human blood:air	<b>17,543</b>	32,836	7,965	---	1,265
Saline:air	<b>5,323</b>	35,869	7,051	---	---

<sup>a</sup>Johanson & Dynesius (1988)

<sup>b</sup>Horton et al. (1992)

<sup>c</sup>Pastino et al. (1997)

- Respiratory uptake will be limited by ventilation rate
- Minimal EG will be exhaled unchanged
- Species/sex differences in blood:air should not be as pronounced as with halogenated solvents

**Battelle**

U.S. Department of Energy  
Pacific Northwest National Laboratory

WV-000000-20

## Tissue:Blood Partition Coefficients

	<b>EG</b>	<b>EGME<sup>a</sup></b>	<b>EGBE<sup>b</sup></b>	<b>MeOH<sup>c</sup></b>	<b>EtOH<sup>d</sup></b>
Liver:blood	<b>0.96</b>	1.02	1.47	1.6	0.81
Kidney:blood	<b>1.22</b>	---	1.84	1.3	---
Fat:blood	<b>0.64</b>	0.05	2.03	1.1	0.11
Muscle:blood	<b>0.57</b>	0.93	0.65	---	0.80

<sup>a</sup>Clarke et al. (1993)

<sup>b</sup>Corley et al. (1994)

<sup>c</sup>Horton et al. (1992)

<sup>d</sup>Pastino et al. (1997)

**Battelle**

U.S. Department of Energy  
Pacific Northwest National Laboratory

WV-000000-30

## Acid Metabolite Tissue:Blood Partition Coefficients

	<b>GA</b>	<b>MAA<sup>a</sup></b>	<b>BAA<sup>b</sup></b>
Liver:blood	0.97	1.26	0.80
Kidney:blood	1.40	---	1.19
Fat:blood	1.09	0.32	0.45
Muscle:blood	0.70	0.50	0.53

<sup>a</sup>Clarke et al. (1993)

<sup>b</sup>Farris (1998)

**Battelle**

U.S. Department of Energy  
Pacific Northwest National Laboratory

WV-000031

## Albino Rat - IV Injection - EG

139 mg <sup>14</sup>C-EG/kg (McChesney et al., 1971)

### EG in tissues 1 hr after dosing

Sample	Observed EG (mg)	Simulated EG (mg)	Ratio (Sim/Obs)
Blood	1.77	1.62	0.91
Lungs	0.28	0.31	1.14
Liver	2.66	0.67	0.25
Kidney	0.18	0.22	1.19

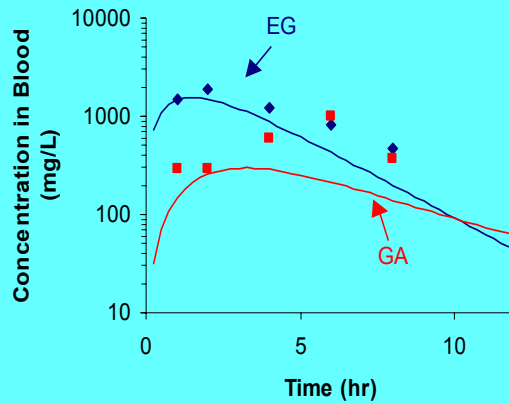
**Battelle**

U.S. Department of Energy  
Pacific Northwest National Laboratory

WV-000032

## Male SD Rat - Oral Gavage - EG

2000 mg/kg (Hewlett et al., 1989)



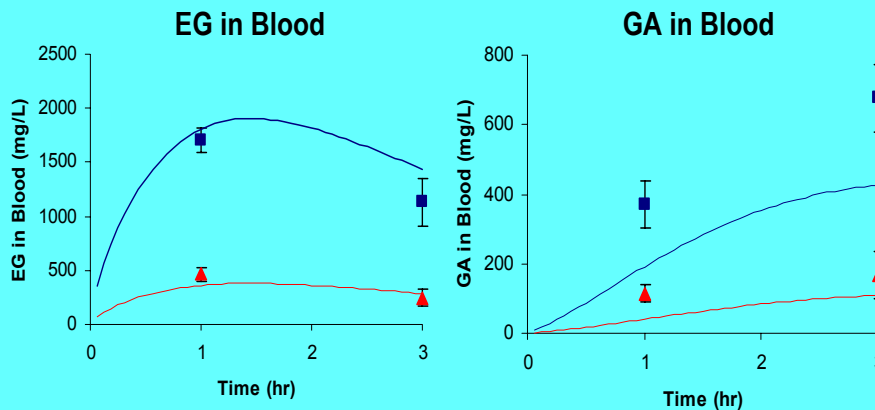
Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 33

## Pregnant SD Rat - Oral Gavage - EG

500 and 1000 mg/kg (Carney et al., 1997)



Battelle

U.S. Department of Energy  
Pacific Northwest National Laboratory

slide 34